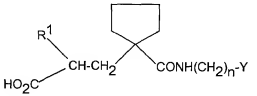
Claims

1 A method of treating female sexual dysfunction comprising administering a therapeutically effective amount of a compound of formula (I), pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof:



(I)

wherein

R^1 is C_{1-6}alkyl which may be substituted by one or more substituents, which may be the same or different, selected from the list: halo, hydroxy, C_{1-6} alkoxy, C_{2-6} hydroxyalkoxy, C_{1-6} alkoxy(C_{1-6}alkoxy), C_{3-7}cycloalkyl, C_{3-7}cycloalkenyl, aryl, aryloxy, (C_{1-4}alkoxy)aryloxy, heterocyclyl, heterocyclyloxy, $-NR^2R^3$, $-NR^4COR^5$, $-NR^4SO_2R^5$, $-CONR^2R^3$, $-S(O)_pR^6$, $-COR^7$ and $-CO_2(C_{1-4}alkyl)$; or R^1 is C_{3-7}cycloalkyl, aryl or heterocyclyl, each of which may be substituted by one or more substituents from said list, which substituents may be the same or different, which list further includes C_{1-6}alkyl; or R^1 is C_{1-6} alkoxy, $-NR^2R^3$ or $-NR^4SO_2R^5$;

wherein

R^2 and R^3 are each independently H, C_{1-4}alkyl, C_{3-7}cycloalkyl (optionally substituted by hydroxy or C_{1-4}alkoxy), aryl, (C_{1-4}alkyl)aryl, C_{1-6}alkoxyaryl or heterocyclyl; or R^2 and R^3 together with the nitrogen to which they are attached form a pyrrolidinyl, piperidino, morpholino, piperazinyl or *N*-(C_{1-4} alkyl)piperazinyl group;

R^4 is H or C_{1-4}alkyl;

R^5 is C_{1-4}alkyl, CF_3, aryl, (C_{1-4} alkyl)aryl, (C_{1-4}alkoxy)aryl, heterocyclyl, C_{1-4}alkoxy or $-NR^2R^3$ wherein R^2 and R^3 are as previously defined;

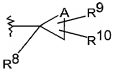
R^6 is C_{1-4}alkyl, aryl, heterocyclyl or NR^2R^3 wherein R^2 and R^3 are as previously defined; and

R^7 is C_{1-4}alkyl, C_{3-7}cycloalkyl, aryl or heterocyclyl; p is 0, 1, 2 or 3;

n is 0, 1 or 2;

the $-(CH_2)_n-$ linkage is optionally substituted by C_{1-4}alkyl, C_{1-4}alkyl substituted with one or more fluoro groups or phenyl, C_{1-4}alkoxy, hydroxy, hydroxy(C_{1-3}alkyl), C_{3-7}cycloalkyl, aryl or heterocyclyl;

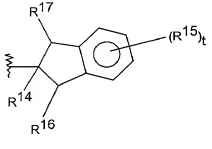
Y is the group



wherein A is $-(CH_2)_q-$ where q is 1, 2, 3 or 4 to complete a 3 to 7 membered carbocyclic ring which may be saturated or unsaturated; R^8 is H, C_{1-6}alkyl, $-CH_2OH$, phenyl, phenyl(C_{1-4}alkyl) or $CONR^{11}R^{12}$; R^9 and R^{10} are each independently H, $-CH_2OH$, $-C(O)NR^{11}R^{12}$, C_{1-6}alkyl, phenyl (optionally substituted by C_{1-4}alkyl, halo or C_{1-4}alkoxy or phenyl(C_{1-4}alkyl) wherein the phenyl group is optionally substituted by C_{1-4}alkyl, halo or C_{1-4}alkoxy, or R^9 and R^{10} together form a dioxolane; $R^{11}$and R^{12} which may be the same or different are H, C_{1-4}alkyl, R^{13} or $S(O)_rR^{13}$, where r is 0, 1 or 2 and R^{13} is phenyl optionally substituted by C_{1-4}alkyl or phenylC_{1-4}alkyl wherein the phenyl is optionally substituted by C_{1-4}alkyl; or

Y is the group, $-C(O)\ NR^{11}\ R^{12}$ wherein R^{11} and R^{12} are as previously defined except that R^{11} and R^{12} are not both H; or

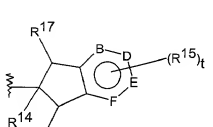
Y is the group,



wherein R^{14} is H, CH_2OH, or $C(O)NR^{11}R^{12}$ wherein R^{11} and R^{12} are as previously defined; when present R^{15}, which may be the same or different

to any other R^{15}, is OH, C_{1-4}alkyl, C_{1-4}alkoxy, halo or CF_3; t is 0, 1, 2, 3 or 4; and R^{16} and R^{17} are independently H or C_{1-4} alkyl; or

Y is the group



wherein one or two of B, D, E or F is a nitrogen, the others being carbon; and R^{14} to R^{17} and t are as previously defined; or

Y is an optionally substituted 5-7 membered heterocyclic ring, which may be saturated, unsaturated or aromatic and contains a nitrogen, oxygen or sulphur and optionally one, two or three further nitrogen atoms in the ring and which may be optionally benzofused and optionally substituted by:

C_{1-6} alkoxy; hydroxy; oxo; amino; mono or di-(C_{1-4}alkyl)amino; C_{1-4}alkanoylamino; or

C_{1-6}alkyl which may be substituted by one or more substituents, which may be the same or different, selected from the list: C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{1-6}alkylthio, halogen, C_{3-7}cycloalkyl, heterocyclyl or phenyl; or

C_{3-7}cycloalkyl, aryl or heterocyclyl, each of which may be substituted by one or more substituents, which may be the same or different, selected from the list: C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}haloalkoxy, C_{1-6}alkylthio, halogen, C_{3-7}cycloalkyl, heterocyclyl or phenyl;

wherein when there is an oxo substitution on the heterocyclic ring, the ring only contains one or two nitrogen atoms and the oxo substitution is adjacent a nitrogen atom in the ring; or

Y is $-NR^{18}S(O)_uR^{19}$, wherein R^{18} is H or C_{1-4}alkyl; R^{19} is aryl, arylC_{1-4}alkyl or heterocyclyl; and u is 0, 1, 2 or 3.

2 A compound of formula (I), pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein R^1, n and Y are as defined in claim 1 with the proviso that Y is not the group $-C(O)NR^{11}R^{12}$ and when R^1 is propyl or phenylethyl, R^{14} is not $-CH_2OH$.

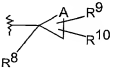
3 A compound of formula (I), pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein R^1, n and Y are as defined in claim 1 with the proviso that Y is not the group $-C(O)NR^{11}R^{12}$ and R^{14} is not H or $-CH_2OH$.

4 A compound according to claim 2 , pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein R^1 is C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxy(C_{1-3})alkyl, C_{1-6}alkoxyC_{1-6}alkoxyC_{1-3}alkyl or C_{1-6}alkyl substituted with aryl.

5 A compound according to claim 4, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein R^1 is C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkoxy(C_{1-3})alkyl or C_{1-6}alkoxyC_{1-6}alkoxyC_{1-3}alkyl.

6 A compound according to claim 5, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein R^1 is C_{1-4}alkyl or C_{1-6}alkoxy(C_{1-3})alkyl.

7 A compound according to claim 2 , pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein when Y is the group



and the carbocyclic ring is fully saturated, then preferably one of R^9 or R^{10} is $-CH_2OH$; $-C(O)NR^{11}R^{12}$; C_{1-6}alkyl; phenyl optionally substituted by C_{1-4}alkyl; or phenyl(C_{1-4}alkyl) wherein the phenyl group is optionally substituted by C_{1-4}alkyl.

8 A compound according to claim 7, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein the carbocyclic ring is 5, 6 or 7

membered wherein one of R^9 or R^{10}, is -C(O)$NR^{11}R^{12}$, with the other being C_{1-6}alkyl; phenyl optionally substituted by C_{1-4}alkyl; or phenyl(C_{1-4}alkyl) wherein the phenyl group is optionally substituted by C_{1-4}alkyl.

9 A compound according to claim 7 , pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein R^9 and R^{10} are attached to adjacent carbon atoms in the ring.

10 A compound according to claim 7 pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein R^8 is CH_2OH.

11 A compound according to claim 2 , pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein when Y is the group -$NR^{18}S(O)_uR^{19}$, preferably R^{18} is H.

12 A compound according to claim 2 , pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein R^{19} is benzyl or phenyl.

13 A compound according to claim 2, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein u is 2.

14 A compound according to claim 2, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein Y is an optionally substituted 5-7 membered heterocyclic ring.

15 A compound according to claim 14, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein the 5-7 membered heterocyclic ring is an optionally substituted aromatic ring.

16 A compound according to claim 15, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein said aromatic ring is pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, indolyl, isoindolinyl, quinolyl, isoquinolyl, pyridonyl, quinoxalinyl or quinazolinyl each of which may be substituted as defined in claim 1.

17 A compound according to claim 16, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein the aromatic ring is oxadiazole, pyridone or thiadiazole each of which may be substituted as defined in claim 1.

18 A compound according to claim 17, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein the aromatic ring is 1,2,5-oxadiazole, 1,3,4-oxadiazole, 2-pyridone or 1,3,4-thiadiazole each of which may be substituted as defined in claim 1.

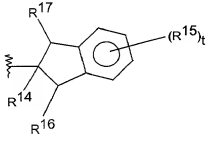
19 A compound according to claim 14 , pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein the 5-7 membered heterocyclic ring is substituted by one or more C_{1-6}alkyl, phenyl or phenylC_{1-4}alkyl.

20 A compound according to claim 19, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein the 5-7 membered heterocyclic ring is substituted by C_{1-4}alkyl or benzyl.

21 A compound according to claim 17, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein when Y is a pyridone said pyridone is *N*-substituted pyridone.

22 A compound according to claim 14, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein Y is a lactam linked at the nitrogen.

23 A compound according to any claim 2, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein Y is

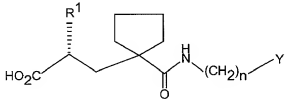


wherein R^{14} is CH_2OH or $C(O)NR^{11}R^{12}$

24 A compound according to claim 2, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein R^{16} and R^{17} are hydrogen.

25 A compound according to claim 2, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, wherein t is 0.

26 A compound of formula Ie, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof,



(Ie)

wherein R^1, Y and n are as defined in claim 2.

27 A compound, pharmaceutically acceptable salts, solvates, polymorphs or prodrugs thereof, selected from the group consisting of:

2-[(1-{[(1-benzyl-6-oxo-1,6-dihydro-3-pyridinyl)amino]carbonyl}cyclopentyl)-methyl]-4-methoxybutanoic acid;

2-{[1-({[3-(2-oxo-1-pyrrolidinyl)propyl]amino}carbonylcyclopentyl]-methyl}-4-phenylbutanoic acid);

(+)-2-{[1-({[2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]amino}carbonyl)cyclopentyl]methyl}-4-phenylbutanoic acid;

2-[(1-{[(5-methyl-1,3,4-thiadiazol-2-yl)amino]carbonyl}cyclopentyl)methyl]-4-phenylbutanoic acid;

cis-3-(2-methoxyethoxy)-2-[(1-{[(4-{[(phenylsulfonyl)amino]carbonyl}cyclohexyl)-amino]carbonyl}cyclopentyl)methyl]propanoic acid;

(+)-2-{[1-({[2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]amino}carbonyl)cyclopentyl]-methyl}pentanoic acid;

(2*R*)-2-[(1-{[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]carbonyl}cyclopentyl)-methyl]pentanoic acid or (-)-2-[(1-{[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]carbonyl}cyclopentyl)-methyl]pentanoic acid;

(2*S*)-2-[(1-{[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]carbonyl}cyclopentyl)-methyl]pentanoic acid or (+)-2-[(1-{[(5-ethyl-1,3,4-thiadiazol-2-yl)amino]carbonyl}cyclopentyl)-methyl]pentanoic acid ;

2-({1-[(3-benzylanilino)carbonyl]cyclopentyl}methyl)pentanoic acid ;
2-[(1-{[(1-benzyl-6-oxo-1,6-dihydro-3-pyridinyl)amino]carbonyl}cyclopentyl)-methyl]pentanoic acid ;
2-{[1-({[(1R,3S,4R)-4-(aminocarbonyl)-3-butylcyclohexyl]amino}carbonyl)-cyclopentyl]methyl}pentanoic acid ;
trans-3-[1-({[2-(4-chlorophenyl)cyclopropyl]amino}carbonyl)cyclopentyl]-2-(methoxymethyl)propanoic acid ;
trans-3-[1-({[2-(4-methoxyphenyl)cyclopropyl]amino}carbonyl)cyclopentyl]-2-(methoxyethyl)propanoic acid ;
trans-3-[1-({[2-pentylcyclopropyl]amino}carbonyl)cyclopentyl]-2-(methoxyethyl)propanoic acid ;
3-[1-({[5-benzyl-[1,3,4]-thiadiazol-2-yl]amino}carbonyl)cyclopentyl]-2-(methoxyethyl)propanoic acid ;
3-[1-({[4-butylpyridin-2-yl]amino}carbonyl)cyclopentyl]-2-(methoxyethyl)propanoic acid ;
3-[1-({[4-phenylpyridin-2-yl]amino}carbonyl)cyclopentyl]-2-(methoxyethyl)propanoic acid ;
3-[1-({[1-hydroxymethyl-3-phenylcyclopentyl]amino}carbonyl)cyclopentyl]-2-(methoxyethyl)propanoic acid ;
2-{[1-({[2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]amino}carbonyl)-cyclopentyl]methyl}-4-methoxybutanoic acid ;
trans-3-[1-({[2-phenylcyclopropyl]amino}carbonyl)cyclopentyl]-2-(methoxyethyl)propanoic acid ;
(*R*)- 2-{[1-({[2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]amino}carbonyl)-cyclopentyl]methyl}-4-methoxybutanoic acid ; and
(*S*)-2-{[1-({[2-(hydroxymethyl)-2,3-dihydro-1*H*-inden-2-yl]amino}carbonyl)-cyclopentyl]methyl}-4-methoxybutanoic acid .

28 The method according to claim 1 wherein the female sexual dysfunction treated includes at least female sexual arousal dysfunction (FSAD).

29 The method according to claim 1 wherein the medicament is administered systemically.

30 The method according to claim 1 wherein the medicament is administered orally.

31 A method of treatment or prophylaxis of a condition for which a beneficial therapeutic response can be obtained by the inhibition of neutral endopeptidase comprising administration of a therapeutically effective amount of a compound as defined in claim 2.

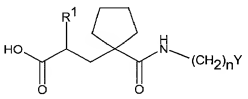
32 A medicine comprising the compound of claim 2.

33 A pharmaceutical formulation including a compound as defined in claim 2 together with a pharmaceutically acceptable excipient.

34 A method for the treatment or prophylaxis of female sexual dysfunction including administering to the patient a therapeutically effective amount of a compound as defined in claim 2.

35 A female sexual dysfunction pharmaceutical formulation including a therapeutically effective amount of a compound as defined in claim 2 together with a pharmaceutically acceptable excipient.

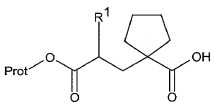
36 A process for preparing a compound of formula I or salts thereof



(I)

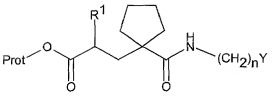
wherein R^1, n and Y are as defined in any one of claims 2 to 27, comprising the steps of:

a) reacting a compound of formula II



(II)

wherein Prot is a suitable protecting group, with a compound of formula $Y(CH_2)_nNH_2$ (III), to give a compound of formula IV,



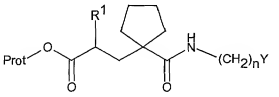
(IV) ;

then

b) reacting the compound of formula IV under suitable deprotecting conditions to give the compound of formula I; then

c) optionally forming a salt.

37. A compound of formula IV



(IV) ,

wherein R^1, n, and Y are as defined in claim 2 and wherein Prot is a protecting group.

Figure 1

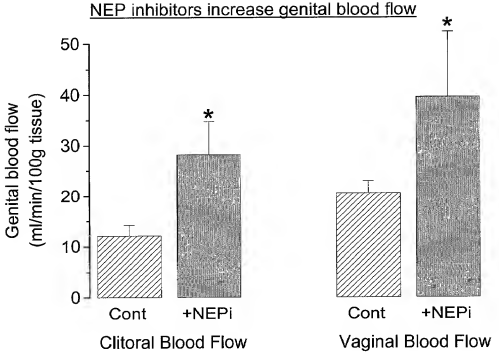


Figure 2